PATENT

ATTY. DOCKET NUMBER: REF/DEHN

THE COMMISSIONER OF PATENTS AND TRADEMARKS
WASHINGTON, DC 20231

Transmitted herewith for filing under *35 USC 111* and *37 CFR 1.53* is the ☐ Design ☒ Utility patent application of:

INVENTOR: Trygve GULBRANDSEN *et al.*

ENTITLED: Process for the Preparation of Contrast Agents

Enclosed are:

☒ 12 pages of written description, claims and abstract.

☐ 0 sheet(s) of drawings.

☒ An assignment of the invention to **NYCOMED IMAGING AS**

☒ Executed declaration of the inventors.

☐ A certified copy of a _____ application. Priority is claimed if not already of record.

☐ A verified statement to establish small entity status under *37 CFR 1.9* and *37 CFR 1.27.*

☒ Preliminary amendment.

☐

The filing fee has been calculated as shown below:

ITEM AS FILED		# EXTRA	SMALL ENTITY	FULL FEE
Basic Fee			☐ Utility $385. ☐ Design $160.	☒ Utility $770. ☐ Design $320.
Total Claims	12 - 20 =	0 [1]	× $ 11 =	× $ 22 = 0
Independent Claims	2 - 3 =	0 [2]	× $ 40 =	× $ 80 = 0
☐ Multiple Dependent Claims in Proper Form Presented			+ $130 =	+ $260 = 0
TOTAL			$	$ 770

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☐ Please charge my **Deposit Account Number 02-0200** in the amount of $_____ to cover the filing fee (and assignment recording fee, if any). A duplicate copy of this paper is enclosed.

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☒ The Commissioner is hereby authorized to charge any additional fees associated with this communication, including patent application filing fees and processing fees under *37 CFR 1.16* and *37 CFR 1.17* or credit any overpayment to **Deposit Account Number 02-0200**. A duplicate copy of this paper is enclosed.

BACON & THOMAS
625 SLATERS LANE - FOURTH FLOOR
ALEXANDRIA, VIRGINIA 22314
(703) 683-0500

DATE: April 21, 1997

Respectfully submitted,

Richard E. Fichter
Attorney for Applicant
Registration Number: 26,382

64974/002.594

Process for the preparation of contrast agents

Field of the Invention

The invention relates to a process for the preparation of iodinated X-ray contrast agents, in particular non-ionic N-alkylated-acylamino-triiodophenyl compounds such as iohexol, iodixanol, iopentol and ioxilan.

Background of the Invention

Non-ionic iodinated X-ray contrast agents have achieved great commercial success over the past twenty years and accordingly improving the efficiency of their manufacture is of great importance.

The manufacture of non-ionic contrast agents includes production of the chemical drug substance (primary production), followed by formulation to drug product (secondary production). The drug substance is usually made in a multistep chemical synthesis, and is thoroughly purified before formulation. As with any commercial drug production it is important to optimize yield, process time and demand for expensive equipment. All these parameters depend both on the chemical reaction conditions and the work-up between each step. The number of steps in the overall synthesis will of course be of great importance and if the work-up between individual process steps could be omitted significant improvement in efficiency can be obtained, provided that sufficient quality and yield are maintained for the final product.

Omitting the work-up between two process steps means that the second step will be performed in the crude

reaction solution resulting from the previous step. Potential major advantages includes:

- higher yield (through avoidance of loss of the intermediate in the work-up);

- elimination of isolation, purification, drying and analysis of the intermediate;

- significant reduction in equipment demand (eg. reactors, filters, driers, etc.); and

- significant reduction of the process time.

Despite these potential advantages, in practice intermediates are usually worked up between successive process steps. The reasons for this often include the facts that impurities may carry through the process and that the optimum solvent for the first reaction is usually not the same as for the second reaction.

The present multistage preparation of certain non-ionic X-ray contrast agents requires successive acylation and N-alkylation reactions. Thus for example in the production of iohexol (as described in SE-7706792-4 and by Gulbrandsen in Kjemi No. 6/90, pages 6-8), 5-amino-N,N'-bis(2,3-dihydroxypropyl)-2,4,6-triiodophthalamide (hereinafter 5-Amine) is acetylated to produce 5-acetamido-N,N'-bis(2,3-dihydroxypropyl)-2,4,6-triiodophthalamide (hereinafter 5-Acetamide) which is then N-alkylated to produce 5-[N-(2,3-dihydroxypropyl)-acetamido]-N,N'-bis(2,3-dihydroxypropyl)-2,4,6-triiodophthalamide (iohexol).

Similarly, in the production of iopentol as described in NO-160918, 5-Amine is acetylated to yield 5-Acetamide which is N-alkylated to produce 5-[N-(2-hydroxy-3-

methoxypropyl)acetamido-N,N'-bis(2,3-dihydroxypropyl)-2,4,6-triiodophthalamide (iopentol).

In the production of iodixanol described in NO-161368, 5-Amine is acetylated to yield 5-Acetamide which is then reacted with a bifunctional alkylating agent, a coupling agent, to yield 1,3-bis(acetamido)-N,N'-bis[3,5-bis(2,3-dihydroxypropylaminocarbonyl)-2,4,6-triiodophenyl]-2-hydroxypropane (iodixanol).

In the preparation of iohexol described above, the acylation is effected in acetic anhydride in the presence of a catalytic amount of sulphuric acid followed by concentration and addition of methanol. Thereafter water and sodium hydroxide (to pH 10-11) are added, base hydrolysis (to remove O-acyl groups) proceeds for 4-5 hours and 5-Acetamide is isolated from the reaction mixture by cooling and neutralization with hydrochloric acid. The precipitated 5-Acetamide is filtered, washed with water and dried. The 5-Acetamide is then dissolved in propylene glycol with the addition of sodium methoxide, the resulting methanol is stripped off and the N-alkylating agent (1-chloro-2,3-propanediol) is added. After the N-alkylation reaction is complete, the reaction mixture is evaporated to dryness and further purification steps (involving crystallization from a further solvent, butanol) are performed to yield the purified iohexol in a form suitable for use in secondary production.

The 5-Amine to 5-Acetamide acylation described for the preparation of iopentol in NO-160918 is similar, with the 5-Amine being acylated in acetic anhydride in the presence of a catalytic amount of p-toluene sulphonic acid. After cooling the reaction mixture, a precipitate forms which is filtered off and suspended in a mixture of methanol and water and hydrolysed under basic

conditions (pH 11.5). The 5-Acetamide product is filtered off after cooling to ambient temperature, neutralization with HCl and further cooling to 3°C. The 5-Acetamide is washed with water and dried before being suspended in propylene glycol. Sodium hydroxide is added and when all solid material has dissolved, the N-alkylating agent (here 1-chloro-3-methoxy-2-propanol) is added. After the alkylation is quenched, several purification steps are again required before satisfactorily pure iopentol is obtained.

For the synthesis of iodixanol described in NO-161368, 5-Acetamide is prepared and worked up as described for iopentol above. It is then suspended in water and dissolved therein with the addition of sodium hydroxide. The N-alkylating agent, the coupling reagent epichlorohydrin, is then added. After the reaction is complete it is quenched with dilute hydrochloric acid and further purification steps are carried out in order to obtain satisfactorily pure iodixanol.

Summary of the Invention

It has now been surprisingly found that the work-up of the 5-Acetamide before the subsequent N-alkylation may be avoided without unacceptable loss in yield or purity of the acylated, N-alkylated product and without undue complication of the purification procedure for that product.

Thus viewed from one aspect the invention provides a process for the preparation of an N-alkyl-acylamino-phenyl-carboxylic acid or carboxylic acid derivative by liquid phase acylation and subsequent N-alkylation of a corresponding amino-phenyl-carboxylic acid (or carboxylic acid derivative) characterised in that said N-alkylation is effected by addition of an alkylating

agent to a solution containing the reaction products of said acylation, ie. those that remain in solution during the liquid phase acylation.

Viewed from an alternative aspect the invention provides a process for the preparation of an N-alkyl-acylamino-phenyl-carboxylic acid or carboxylic acid derivative compound comprising acylating an amino-phenyl-carboxylic acid (or carboxylic acid derivative) in a liquid phase, base hydrolysing the acylated product to remove O-acyl groups from the N-acyl-amino intermediate and, maintaining the liquid phase at a basic pH, N-alkylating the N-acylamino intermediate.

Detailed Description of the Invention

In the process of the invention, the aminophenyl carboxylic acid or carboxylic acid derivative starting product is preferably a compound having a total of three amino and carboxyl groups on the phenyl ring, eg. an aminoisophthalic acid or derivative or a diaminobenzoic acid or derivative. By carboxylic acid derivative is meant for example a salt, ester or amide, eg. an CONHR* or COOR* group where R* is optionally hydroxylated alkyl preferably optionally hydroxylated C_{1-6} alkyl. Furthermore the starting compound is preferably a triiodophenyl compound, particularly an alkylamino-carbonyl-triiodophenyl compound and most particularly a 2,4,6-triiodo-2,5-bis(alkylamino-carbonyl)-aniline, such as 5-Amine for example. The alkyl moiety of any alkylaminocarbonyl group will preferably carry one or more hydroxyl groups and will typically contain up to 6, preferably up to 4 carbon atoms.

The acylation of the starting compound may be effected using any convenient acylating agent, eg. an acetylating agent such as for example an acid halide or more

preferably acetic anhydride.

Following the acylation, which is conveniently acid catalysed, the product is base hydrolysed, eg. at pH 11 to 12, to remove unwanted O-acyl groups without displacing the desired N-acyl groups. Base hydrolysis may be with any organic or inorganic base but is preferably effected using an inorganic base, eg. an alkali metal hydroxide such as sodium hydroxide.

After the base hydrolysis, the solution pH is if necessary adjusted to an appropriate basic value for N-alkylation (generally within the range 10-12), and if desired further solvent (eg. a lower alcohol such as a C_{1-4} alcohol, eg. methanol, optionally together with water) is added to the reaction mixture before, during or after addition to the reaction mixture of the alkylating agent, thereby ensuring that the non-isolated intermediate does not precipitate out.

Thus unlike prior successive acylation and N-alkylation reactions, the reaction medium is maintained at a basic pH and the N-acylated product (and the by-products) are not isolated from the reaction mixture before the subsequent N-alkylation step.

The N-alkylating agent used in the N-alkylation of the non-isolated intermediate may be any alkylating agent capable of introducing the desired alkyl group (or a precursor for a desired group) at the acylamino nitrogen. Where the acylated, N-alkylated product is intended to be a dimer (ie. containing two iodophenyl groups), the alkylating agent may be a bifunctional coupling agent.

For the preparation of iohexol, 1-halo-2,3-propanediols (eg. 1-chloro-2,3-propanediol) and glycidol are

preferred alkylating agents. For the preparation of iopentol, 1-halo-3-methoxy-2-propanols (eg. 1-chloro-3-methoxy-propanol) are preferred. For the production of iodixanol a coupling agent such as a 1,3-halo-2-propanol or more preferably epichlorohydrin may be used.

The alkylation reaction may be terminated conventionally by quenching with acid, eg. HCl, and the acetylated, N-alkylated product may also be worked up conventionally, eg. by crystallization from an appropriate solvent or solvent mixture, eg. one or more C_{1-6} alcohols.

Where the N-alkyl-acylamino product is a product such as iohexol, iopentol or iodixanol, this work-up yields a product which can be used for secondary production of an X-ray contrast medium. However for other end products, the product may be used as the starting material for further synthetic steps, eg. in the primary production of a non-ionic X-ray contrast agent.

Thus the process of the present invention allows N-acylation and N-alkylation to be effected as a one-pot synthesis achieving savings in equipment, time and materials without undue loss in yield and, surprisingly, achieving in the purification of the end product comparable or better purity levels to those achieved when the intermediate and the end product are both subject to work up stages.

The process of the present invention is particularly applicable to the preparation of the following N-alkyl-acylaminophenyl X-ray contrast agents: iomeprol, ioversol, ioxilan, iotrolan, ioxaglate, iodecimol, 2-iopyrol, 2-iopiperidol, iohexol, iopentol and iodixanol.

The invention will now be illustrated further by reference to the following non-limiting Examples.

EXAMPLE 1

5-Amino-N,N'-bis(2,3-dihydroxypropyl)-2,4,6-triiodoisophthalamide (388 g), acetic anhydride (838 g) and *p*-toluene sulfonic acid (2 g) were mixed and heated to reflux for 1.5 hours, before concentration to a highly viscous solution under reduced pressure. Methanol (44 g) was added to the solution in several portions with distillation under atmospheric pressure between each addition, followed by a final portion of methanol (266 g). A small amount of distilled water (40 ml) was added before stirring at 55°C overnight.

A portion (490 ml) of a solution made as described above was added to a jacketed reactor at about 30°C, and stirred with a speed of 150 rpm. The pH was raised by aqueous sodium hydroxide (50 w/v%, 190 ml) to about 12. 1-Chloro-2,3-propanediol (49 g) was added to the solution, and the pH was further adjusted by sodium hydroxide (50 w/v%, 25 ml) to about 11.5. Small amounts of additional 1-chloro-2,3-propanediol (total 6 ml) were added during the first 24 hours of the reaction. After a total reaction time of 99 hours, the solution was analyzed by reversed phase HPLC (water/acetonitrile as eluent) with the following results:

Iohexol	94.4%
5-Acetamide	1.9%
5-Amine	0.6%
Other impurities	3.1%

EXAMPLE 2

5-Amino-N,N'-bis(2,3-dihydroxypropyl)-2,4,6-triiodoisophthalamide (388 g), acetic anhydride (838 g) and *p*-toluene sulfonic acid (2 g) were mixed and heated to reflux for 1.5 hours, before concentration to a

highly viscous solution under reduced pressure. Methanol (44 g) was added to the solution in several portions with distillation under atmospheric pressure between each addition, followed by a final portion of methanol (266 g). A small amount of distilled water (40 ml) was added before stirring at 55°C overnight.

A portion (490 ml) of a solution made as described above was added to a jacketed reactor at about 35°C, and stirred with a speed of 150 rpm. The pH was raised by aqueous sodium hydroxide (50 w/v%, 200 ml) to about 12. Additional sodium hydroxide solution (10 ml) and 1-chloro-3-methoxy-2-propanol (42 g) were added, and the pH was adjusted back to about 12 by small amounts of sodium hydroxide solution. Further additions of 1-chloro-3-methoxy-2-propanol (total 21 g) were added after 2, 3, 4, 5 and 6 hours of reaction. After a total reaction time of 53 hours, the mixture was analyzed by HPLC (water/acetonitrile as eluent) with the following results:

Iopentol	91.4%
5-Acetamide	1.6%
5-Amine	0.3%
Other impurities	6.8%

Claims:

1. In a process for the preparation of an N-alkyl-acylamino-phenyl-carboxylic acid or carboxylic acid derivative by liquid phase acylation and subsequent N-alkylation of a corresponding amino-phenyl-carboxylic acid (or carboxylic acid derivative), the improvement comprising the addition of an alkylating agent to a solution containing the reaction products of said acylation, to effect said N-alkylation.

2. A process as claimed in claim 1 wherein said corresponding amino-phenyl carboxylic acid (or carboxylic acid derivative) is a compound having a total of three amino and carboxyl groups on the phenyl ring thereof.

3. A process as claimed in claim 1, wherein said corresponding amino-phenyl-carboxylic acid (or carboxylic acid derivative) is a triiodophenyl compound.

4. A process as claimed in claim 1, wherein said corresponding amino-phenyl-carboxylic acid (or carboxylic acid derivative) is an alkylamino-carbonyl-triiodophenyl compound.

5. A process as claimed in claim 1, wherein said corresponding amino-phenyl-carboxylic acid (or carboxylic acid derivative) is a 2,4,6-triiodo-2,5-bis(alkylamino-carbonyl)-aniline.

6. A process as claimed in claim 1, wherein said corresponding amino-phenyl-carboxylic acid (or carboxylic acid derivative) is 5-amino-N-N'-bis(2,3-dihydroxypropyl)-2,4,6-triiodophthalamide.

7. A process as claimed in claim 1, wherein said corresponding amino-phenyl-carboxylic acid (or carboxylic acid derivative) contains an alkylaminocarbonyl group carrying one or more hydroxyl groups and containing up to 6 carbon atoms.

8. A process as claimed in claim 1, wherein said acylation is effected using an acid halide or acetic anhydride.

9. A process as claimed in claim 1, wherein said alkylating agent is selected from the group consisting of 1-halo-2,3-propanediols, glycidol, 1-halo-3-methoxy-2-propanols, 1,3-halo-2-propanols and epichlorohydrin.

10. A process for the preparation of an N-alkyl-acylamino-phenyl-carboxylic acid or carboxylic acid derivative compound comprising acylating an amino-phenyl-carboxylic acid (or carboxylic acid derivative) in a liquid phase, base hydrolysing the acylated product to remove O-acyl groups from the resulting N-acyl-amino intermediate and, maintaining the liquid phase at a basic pH, N-alkylating said N-acylamino intermediate.

11. A process as claimed in claim 1 or claim 10, being a process for the preparation of a contrast agent selected from the group consisting of iomeprol, ioversol, ioxilan, iotrolan, ioxaglate, iodecimol, 2-iopyrol, 2-iopiperidol, iohexol, iopentol and iodixanol.

Summary

Process for the preparation of contrast agents

The invention provides a process for the preparation of an N-alkyl-acylamino-phenyl-carboxylic acid or carboxylic acid derivative by liquid phase acylation and subsequent N-alkylation of a corresponding amino-phenyl-carboxylic acid (or carboxylic acid derivative), the improvement comprising the addition of an alkylating agent to a solution containing the reaction products of said acylation, to effect said N-alkylation.

ATTORNEY/DOCKET NO: **REF/Dehn**

DECLARATION FOR PATENT APPLICATION AND APPOINTMENT OF ATTORNEY

As a below named inventor, I hereby declare that my residence, post office address and citizenship are as stated below next to my name; I believe that I am the original, first and sole inventor (if only one name is listed below) or an original, first and joint inventor (if plural names are listed below) of the subject matter which is claimed and for which a patent is sought on the invention (Design, if applicable) entitled:
PROCESS FOR THE PREPARATION OF CONTRAST AGENTS

the specification of which (check one):

☒ is attached hereto, or ☐ was filed on: as U.S. Application Number or PCT International Application Number:
and (if applicable) was amended on:

I hereby state that I have reviewed and understand the contents of the above-identified specification, including the claims, as amended by any amendment(s) referred to above. I acknowledge the duty to disclose information which is material to patentability as defined in *Title 37, Code of Federal Regulations, §1.56*. I hereby claim foreign priority benefits under *Title 35, United States Code §119* of any foreign application(s) for patent or inventor's certificate listed below and have also identified below any foreign application for patent or inventor's certificate having a filing date before that of the application on which priority is claimed.

PRIOR FOREIGN APPLICATION(S)			PRIORITY CLAIMED	
Number	Country	Day/Month/Year Filed	Yes	No
96 18055.9	Great Britain	29 August 1996	X	

☐ Additional Priority Application(s) Listed on Following Page(s)

I HEREBY CLAIM THE BENEFIT UNDER TITLE 35 U.S. CODE §119(E) OF ANY U.S. PROVISIONAL APPLICATIONS LISTED BELOW.	
Application Number	Day/Month/Year Filed
60/029,143	21 October 1996

☐ Additional Provisional Application(s) Listed on Following Page(s)

I hereby claim the benefit under *Title 35, United States Code, §120* of any United States application(s) or PCT international application(s) designating The United States of America listed below and, insofar as the subject matter of each of the claims of this application is not disclosed in that/those prior application(s) in the manner provided by the first paragraph of *Title 35, United States Code, §112*, I acknowledge the duty to disclose information which is material to patentability as defined in *Title 37, Code of Federal Regulations, §1.56* which became available between the filing date of the prior application(s) and the national or PCT international filing date of this application:

Application Number	Filing Date	Status - Patented, Pending or Abandoned

☐ Additional US/PCT Priority Application(s) listed on Following Page(s)

I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under *section 1001 of title 18 of the United States Code* and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.

POWER OF ATTORNEY: I (We) hereby appoint as my (our) attorneys, with full powers of substitution and revocation, to prosecute this application and transact all business in the Patent and Trademark Office connected therewith: J. Ernest Kenney, Reg. No. 19,179; Eugene Mar, Reg. No. 25,893; Richard E. Fichter, Reg. No. 26,382; Charles R. Wolfe, Jr., Reg. No. 28,680; Thomas J. Moore, Reg. No. 28,974; Bruce H. Troxell, Reg. No. 26,592; and

I(we) authorize my(our) attorneys to accept and follow instructions from _____ regarding any matter related to the preparation, examination, grant and maintenance of this application, any continuation, continuation-in-part or divisional based thereon, and any patent resulting therefrom, until I(we) or my(our) assigns withdraw this authorization in writing.

Send correspondence to: **BACON & THOMAS**
625 Slaters Lane - 4th Floor
Alexandria, VA 22314

Telephone Calls to: **Richard E. Fichter**
(703) 683-0500

FULL NAME OF FIRST OR SOLE INVENTOR	CITIZENSHIP
Trygve GULBRANDSEN	**Norwegian**
RESIDENCE ADDRESS c/o Nycomed Imaging AS Nycoveien 1-2, N-0401 Oslo 4, Norway	POST OFFICE ADDRESS IS THE SAME AS RESIDENCE ADDRESS UNLESS OTHERWISE SHOWN BELOW
DATE April 10, 1997	SIGNATURE Trygve Gulbrandsen

☒ *See following page(s) for additional joint inventors.*

ATTORNEY/DOCKET NO: **REF/Dehn**

CONTINUATION OF DECLARATION FOR PATENT APPLICATION AND APPOINTMENT OF ATTORNEY

FULL NAME OF JOINT INVENTOR **Odd Einar INGVOLDSTAD**	CITIZENSHIP **Norwegian**
RESIDENCE ADDRESS c/o Nycomed Imaging AS Nycoveien 1-2, N-0401 Oslo 4, Norway	POST OFFICE ADDRESS IS THE SAME AS RESIDENCE ADDRESS UNLESS OTHERWISE SHOWN BELOW
DATE 08.04.1997	SIGNATURE Odd E. Ingvoldstad

FULL NAME OF JOINT INVENTOR **Lars Terje HOLMAAS**	CITIZENSHIP **Norwegian**
RESIDENCE ADDRESS c/o Nycomed Imaging AS Nycoveien 1-2, N-0401 Oslo 4, Norway	POST OFFICE ADDRESS IS THE SAME AS RESIDENCE ADDRESS UNLESS OTHERWISE SHOWN BELOW
DATE 4/4-97	SIGNATURE Lars Terje Holmaas

FULL NAME OF JOINT INVENTOR	CITIZENSHIP
RESIDENCE ADDRESS	POST OFFICE ADDRESS IS THE SAME AS RESIDENCE ADDRESS UNLESS OTHERWISE SHOWN BELOW
DATE	SIGNATURE

FULL NAME OF JOINT INVENTOR	CITIZENSHIP
RESIDENCE ADDRESS	POST OFFICE ADDRESS IS THE SAME AS RESIDENCE ADDRESS UNLESS OTHERWISE SHOWN BELOW
DATE	SIGNATURE

☐ *See following pages for additional joint inventors/priority applications.*

PATENT

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of:

Trygve GULBRANDSEN *et al.*

Filed: Herewith on April 21, 1997

For: PROCESS FOR THE PREPARATION OF CONTRAST AGENTS

Attention: Applications Branch

PRELIMINARY AMENDMENT

Assistant Commissioner for Patents
Washington, D.C. 20231

Sir:

Prior to an examination on the merits, please amend the above identified application as follows:

IN THE CLAIMS:

Claim 11, line 1, delete "or claim 10".

Please add the following claim to the application:

--12. A process as claimed in claim 10, being a process for the preparation of a contrast agent selected from the group consisting of iomeprol, ioversol, ioxilan, iotrolan, ioxaglate, iodecimol, 2-iopyrol, 2-iopiperidol, iohexol, iopentol and iodixanol.--

REMARKS

Applicants have amended the claims in order to remove the multiple dependency from claim 11 and reintroduce the cancelled subject matter as new claim 12.

Respectfully submitted,

Richard E. Fichter
Registration No. 26,382

BACON & THOMAS
625 Slaters Lane - 4th Fl.
Alexandria, Virginia 22314
Phone: (703) 683-0500
REF:TJL:tl

April 21, 1997